REMARKS

Upon entry of the requested amendments, claims 1-5, 11, 14, and 21-27 will be pending in this application. Claims 15-20 have been withdrawn.

Applicants have amended claims 4 and 5 to refer to added claim 21. Support for these amendments can be found in the specification , for example, on page 24 and 41, respectively.

Applicants have added claims 21-27. Support for claims 21-24 can be found in the specification as originally filed, for example, on page 7, lines 1-11[1]. Additional support for claim 22 can be found in the Specification on page 23, lines 27-30. Support for claim 25 can be found on page 7, lines 20-26. Support for claims 26 and 27 can be found, for example, in the claims as originally filed.

Priority

The Examiner has stated that the filing dated of the instant application has been deemed to be the filing date of PCT/FR97/02412 because a translation of the French priority document has not been submitted. Applicants have filed herewith a certified copy of the French priority document (FR 96/16207) and the Statement of Scott D. Miller which states that application serial number 09/331,980 (the instant application) is an accurate translation of FR 96/16207. Accordingly, the priority date of the instant application should be deemed to be December 30, 1996.

Substitute Specification and Entry of Amendments

In paragraphs 5 and 6 of the August 27, 2003 Office Action, the Examiner states that the substitute specification filed 10/21/02 has been entered but that the request to amend the specification (filed 11/20/02) has not been entered. Upon review of the file, it appears to applicants that the 10/21/02 Amendment After Final was filed with a substitute specification that incorporated the requested amendments (also see the 10/21/02 Verified Statement). The Examiner, however, did not enter the 10/21/02 amendment but does appear to have accepted the

1 Page and line numbers refer to the pages and lines of the substitute specification filed October 21, 2002.

substitute specification. Accordingly, when the 11/20/02 RCE requested that the 10/21/02 amendment be entered, the page citations in the 10/21/02 Amendment did not match up with the substitute specification because the 10/21/02 Amendment was directed towards the application as it existed prior to entry of the substitute specification (and, in fact, all of the requested amendments were already in the substitute specification). If the Examiner believes it would be easier to contact the undersigned attorney by telephone in order to reconcile this situation, he is invited to do so.

Rejections Under 35 U.S.C. §112, first paragraph

Claims 1-5, 11 and 14 stand rejected under 35 U.S.C. §112, first paragraph. Specifically, the Examiner contends that the specification does not enable the claimed class of antibodies, compositions and kits. In that respect, the Examiner contends that the specification discloses "only two polyclonal antibodies that bind specifically to nitrosylated cysteine-glutaraldehyde conjugated to BSA (NO-Tyr-BSA or NO-Cys-BSA) for in vitro or in vivo detection assays". The Examiner then cites several references in supposed support of the contention that there is an unpredictability to antibody generation and design.

As an initial matter, the instant application does not just disclose detection systems but, in fact, discloses data in two different experimental diseases in vivo: autoimmune encephalitis and inflammatory arthritis (i.e. page 54, line 25 – page 66, line 10). Thus, the *in vitro* data has been extended and confirmed *in vivo*. Data such as this that is absolutely convincing to one of skill in the art that the antibodies have efficacy *in vivo*.

Further, in order to satisfy the enablement requirement of § 112, it is not necessary or desirable for applicants to supply the conditions for each and every antibody that could possibly be included in their claimed invention. Enablement does require, however, that the specification teach one of skill in the art how to practice the invention as claimed without undue experimentation. In re Wands, 8 USPQ2D 1400, 1404 (Fed. Cir. 1988).

It is well established that the enablement requirement is met even if routine experimentation is necessary in order to practice the invention. *Id.* At 1402. There, the Court

stated, "enablement is not precluded by the necessity for some experimentation such as routine screening .... Experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not experimentation.'" *Id.* At 1404. Whether experimentation rises to the level of undue is not a simple factual determination but rather requires a weighing of the Forman factors. *Id.* At 1404.

> "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art....The test is not merely quantitative, since a considerable amount of experimentation is permissible.... The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims."

If the Examiner considers the eight Forman factors, it is clear the present application, to the extent necessary, enables the preparation of antibodies as used in this invention.

For example, a factor to be considered is the quantity of experimentation necessary to practice the invention. Practitioners in the art of antibody preparation expect to practice substantial routine experimentation to arrive at and optimize the variables inherent in this feld. The present situation is very similar to the field of monoclonal antibodies considered by the Federal Circuit in *In re Wands.* In re Wands, 8 USPQ2d 1400, (Fed. Cir. 1988). There, the Court held that screening of a large number of negative hybridomas does not render the field unpredictable, because "practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Id* at 1406. Similarly, practitioners in the field of antibody design are prepared to screen large numbers of antibodies to find those which yield the desired results.

Applicants have provided a number of example antibodies that fall within the scope of the claimed invention. It would not be feasible for applicants to provide similar details on every antibody which may be designed according to the teachings of the present invention. This would require a specification of immense length. Considering the specification in light of the vast

amount of knowledge about antibody design and preparation in the art (including the various textbooks and laboratory manuals cited by the Examiner), one of skill in the art can practice applicants' invention. The Examiner has provided no scientific reason why applicants should be limited to the antibodies disclosed in the examples of the instant specification. For all of these reasons, this rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

Claim 1-5 and 11 stand rejected under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner contends that the phrase "antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in a subject" is new matter. The Examiner contends that applicants have "not pointed out the support for said phrase". Support for this phrase can be found on page 1, lines 14-17 and lines 29-32 (wherein the specification describes pharmaceutical compositions and their use in the treatment of pathologies involving nitric oxide, its derivatives and conjugates and then describes that nitric oxide produced in large quantities or in insufficient amounts is involved in a large number of pathophysiological processes and its action is often relayed through derivatives and conjugates); and page 18, lines 29-30 (wherein the specification describes that implicated pathophysiological processes occur in subjects). Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections Under 35 U.S.C. §102(a)

Claims 1-4 and 11 stand rejected under 35 U.S.C. §102(a) as being anticipated by Mnaimneh et al. (published January 1, 1997). However, applicants have filed herewith (1) a certified copy of priority document FR 96/16207, and (2) a Statement of Scott D. Miller which states that the PCT/FR97/02412 is an accurate translation of FR 96/16207. The instant application therefore properly claims a priority date of December 30, 1996. Accordingly, Mnaimneh et al. is not a qualifying reference under 35 U.S.C. §102(a). Applicants respectfully request that the examiner reconsider and withdraw the rejection under 35 U.S.C. §102(a).

Rejection under 35 U.S.C. §102(b)

Claims 1-4 stand rejected under 35 U.S.C. §102(b) as being anticipated by Boullerne et

al. Specifically, the Examiner contends that Boullerne et al. teach "a purified antibody that recognizes and binds specifically to a nitrosylated protein such as nitrosylated bovine serum albumin." Boullerne et el. describes experiments with sera from patients with multiple sclerosis (MS). Boullerne et al. purports to demonstrate that antibodies found in MS patients are reactive with chemically defined nitroso-amino acids conjugated to a carrier. Boullerne demonstrate this by using ELISA. The Examiner contends that in so doing, Boullerne teaches a purified antibody that recognizes and binds specifically to a nitrosylated protein such as nitrosylated bovine serum albumin. The Examiner further contends that Boullerne teaches that the referenced antibody can be purified using nitrosylated carrier protein or a nitrosylated amino acid coupled to a carrier. The Examiner further contends that Boullerne teaches that NO production may be involved in autoimmune diseases. Applicants traverse.

Boullerne et al. themselves describe what their paper teaches:

> In the present study we analysed sera from MS patients to determine whether or not they may contain circulating antibodies directed against possible NO-modified epitopes by testing them with chemically defined nitroso-amino acids conjugated to carrrier protein by ELISA. Page 118, first column.

Boullerne et al. conclude that the paper for the first time demonstrates the "detection" of specific antibodies in MS sera capable of reacting with NO-Cys-g-BSA. Page 122, column 1.

Contrary to the Examiner's assertion, Boullerne et al. do not purify antibodies. Further, Boullerne does not describe the *in vivo* analyses performed by the inventors in the instant application – the Examiner has admitted such analyses to be important in his rejection under 35 U.S.C. §112. Accordingly, while Boullerne et al. may describe an analysis of sera from MS patients, no where does the reference teach the purified antibodies of the instant invention.

Rejection under 35 U.S.C. §103(a)

Claims 1, 5 and 14 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Mnaimneh et al. (published January 1, 1997) in view of various other references. However, as described above, applicants have filed herewith (1) a certified copy of priority document FR

96/16207, and (2) a Statement of Scott D. Miller which states that the PCT/FR97/02412 is an accurate translation of FR 96/16207. The instant application therefore properly claims a priority date of December 30, 1996. Accordingly, Mnaimneh et al. is not a qualifying reference under 35 U.S.C. §102(a). Applicants respectfully request that the examiner reconsider and withdraw the rejection under 35 U.S.C. §102(a).

Claims 1, 5, 11 and 14 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Boullerne et al. or Stamler et al. each in view of various cited references including Mnaimneh et al. Applicants traverse.

As described above, Boullerne et al. is directed towards the analysis of sera from MS patients to determine whether or not they may contain circulating antibodies directed against possible NO-modified epitopes. This is accomplished by testing them with chemically defined nitroso-amino acids conjugated to carrier protein by ELISA. Page 118, first column. This disclosure does not suggest the purified antibodies of the instant invention, nor their use in pharmaceutical compositions and kits.

Stamler et al. does not make up for this deficiency in Boullerne et al. Stamler et al. merely presents "data showing that a variety of proteins of biological significance and relative abundance can by S-nitrosylated." As stated by the authors, "[t]hese observations raise the possibility that's-nitrosothiol groups in proteins may serve as intermediates in the cellular metabolism or bioactivity of NO and that their formation may represent an important cellular regulatory mechanism."

Mnaimneh et al., as described above, is not a qualifying prior art reference as it was published after the effective filing date of the instant application. The additional references merely describe antibody technology and other related aspects.

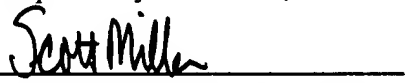
In order to establish a *prima facie* case of obviousness, the Examiner must establish that (1) the combination of references produces the claimed invention, and (2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed.Cir.1991). The Examiner has not established either of these two points. Accordingly, the applicants respectfully request

that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103(a).

CONCLUSION

Applicants believe that the claims are in condition for allowance. If the Examiner has any questions, he is invited to contact the undersigned by telephone.

Respectfully submitted,



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